## Case Report

# An fMRI, DTI and Neurophysiological Examination of Atypical Organization of Motor Cortex in Ipsilesional Hemisphere Following Post-Stroke Recovery

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Objectives: We report a 61-year-old woman who developed left hemiparesis following a right frontal stroke. She underwent rehabilitation and regained function of the left side of her body. Three years after her first stroke, she developed a large left subdural hematoma and again presented with left hemiparesis. Materials and Methods: Prior to the cranioplasty, an fMRI scan involving left and right hand movement, arm movement, and foot peddling were conducted in order to determine whether the patient showed ipsilateral activation for the motor tasks, thus explaining the left hemiparesis following the left subdural hematoma. Diffusion tensor imaging (DTI) tractography was also collected to visualize the motor and sensory tracts. Results: The fMRI results revealed activation in the expected contralateral left primary motor cortex (M1) for the right-sided motor tasks, and bilateral M1 activation for the left-sided motor tasks. Intraoperative neurophysiology confirmed these findings, whereby electromyography revealed left-sided (i.e., ipsilateral) responses for four of the five electrode locations. The DTI results indicated that the corticospinal tracts and spinothalamic tracts were within normal limits and showed no displacement or disorganization. Conclusions: These results suggest that there may have been reorganization of the M1 following her initial stroke, and that the left hemisphere may have become involved in moving the left side of the body thereby leading to left hemiparesis following the left subdural hematoma. The findings suggest that cortical reorganization may occur in stroke patients recovering from hemiparesis, and specifically, that components of motor processing subserved by M1 may be taken over by ipsilateral regions.

Key Words: Stroke—Reorganization—Motor cortex—Recovery—fMRI— Ipsilateral hemisphere

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### Introduction

Motor deficits are common following stroke, often resulting in mild to severe hemiparesis contralateral to the side of the stroke. At least some degree of motor recovery can occur through rehabilitation, and it is widely considered to be a result of cortical reorganization. That is, restoration of motor function may be due to neural plasticity, whereby functions previously performed by the ischemic area are assumed by other ipsilateral or contralateral brain areas.<sup>1–4</sup> Laterality shifts in brain activation, whereby the ipsilateral hemisphere (i.e., contralesional) or bilateral hemispheres are involved in motor movements, have stimulated interest in the role of the unaffected hemisphere in motor recovery (see<sup>5,6</sup> for reviews). The findings that the unaffected hemisphere may play a role in motor recovery following stroke have

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important implications for rehabilitation and our understanding of neural plasticity.

The past several decades have produced substantial evidence in human and non-human primates for the potential of ipsilateral recruitment of motor regions. In a classic study involving Japanese monkeys, a portion of neurons in the precentral motor (8%), supplementary motor (4%), and premotor (9%) cortices had observed activation in response to movement in the hand ipsilateral to the measured neuron.<sup>7</sup> Although activation in the majority of neurons was primarily in response to contralateral hand movement, this small portion of ipsilaterally sensitive neurons demonstrates the potential for a same side relationship between brain and limb. Supporting these findings, an early fMRI study involved ten healthy human subjects performing a finger tapping task.<sup>8</sup> Their results revealed at least some degree of ipsilateral activation in the primary motor cortex (M1), supplementary motor area (SMA), premotor cortex (PMC), and anterior superior parietal cortex. More recent studies investigating the cortical mechanisms involved in the cross-education effect (i.e., the performance improvement of the untrained limb after a period of unilateral practice of the homologous contralateral limb) have found fMRI activation in ipsilateral motor and sensory regions (e.g., premotor cortex, prefrontal cortex, and sensorimotor cortex)<sup>9</sup> and in the temporal lobe.<sup>10</sup> These increases in ipsilateral activation for motor movements of an untrained limb after unilateral training suggest that information in the trained hemisphere might be accessed during execution of the task with the untrained limb. In a clinical PET study,<sup>11</sup> the laterality of motor functions was examined in six stroke patients several months after their recovery. In these patients, the movement of their unaffected hand resulted in primarily contralateral M1 activation. However, in the recovered hand, activation was observed both contralaterally (i.e., recovered hemisphere) and ipsilaterally (i.e., unaffected hemisphere) in M1, SMA, and PMC. In a similar PET study by Chollet et al.,<sup>11</sup> when stroke subjects moved the fingers of the recovered hand, significant regional cerebral blood flow increases were observed in both contralateral and ipsilateral primary sensorimotor regions. Other regions such as insula, inferior parietal lobule, and PMC were also bilaterally activated with movement of the recovered hand. Another PET study<sup>12</sup> investigated brain activity during hand movement in two patients with hemiparesis due to stroke, who showed relatively good motor recovery. They found increased regional cerebral blood flow in the ipsilateral hemisphere during the movement of the recovered hand in stroke patients. Lastly, an fMRI study<sup>13</sup> found that during recovered hand finger-tapping, stroke subjects showed increased activation in the ipsilateral (i.e., unaffected) hemisphere in sensorimotor areas, PMC, and SMA compared with controls. These studies provide early examples of the ability for the contralesional

hemisphere to be recruited for motor function during and post-recovery.

Rehabilitative and treatment focused studies have also described evidence supporting the recruitment of the unaffected hemisphere during stroke recovery. In one study evaluating the validity of electrical neuromuscular stimulation as a treatment option to improve patient recovery post-stroke, Kimberly et al.<sup>14</sup> observed increased intensity of activation in the contralesional hemisphere after applying neuromuscular stimulation to the affected hand for several sessions over a period of three weeks. Treatment focused studies by Kim et al.<sup>15</sup> and Schaechter et al.<sup>16</sup> used fMRI to study the effect of short term constraint-induced movement therapy (CIMT) on activation of the motor network. Both studies found that CIMT improved motor function of the paretic limb for patients, and showed increased activation in the ipsilateral M1 and SMA. These findings suggest that improvements in motor function of the affected upper extremity may be associated with a relative increase in activation of motor cortices of the undamaged hemisphere during affected hand movement. However, the evidence for ipsilateral recruitment during motor tasks is not exclusive to upper limb movement. A study by Carey et al.<sup>17</sup> used fMRI to examine whether ankle-movement tracking training could improve ankle function and brain reorganization. From pre-test to post-test, they found an increase in activation in multiple neural areas including contralateral and ipsilateral motor regions. These results suggest that the brain's capacity to reorganize is sufficiently robust to respond not only to intensive upper limb tracking training,<sup>18</sup> but lower limb training as well.

While patterns of brain network reorganization vary across stroke patients, higher activation in contralesional M1 and bilateral premotor areas in stroke patients compared to healthy controls emerged as a highly-consistent finding in a recent meta-analysis of over 50 neuroimaging studies.<sup>19</sup> Initial early hyperexcitability of the homologous M1 commonly occurs in stroke patients<sup>11,20,21,22</sup> and may initially contribute to recovery, as demonstrated in both human and animal models.<sup>23,24,25</sup> Yet overall, cross-sectional and longitudinal studies have demonstrated that well-recovered stroke patients tend to rely unilaterally on the original ipsilesional network on motor tasks (i.e., gradual increases in M1 ipsilesional activation and reduced bilateral activation) as compared to ill-recovered patients.<sup>11,19,26,27,28</sup> For instance, well-recovered stroke patients in a cross-sectional study<sup>27</sup> demonstrated a shift from bilateral activation to unilateral activation during movements of the hand. Supporting these findings, Foltys et al.<sup>29</sup> also noted fMRI activation in ipsilateral motor regions for simple motor tasks.

For a subset of well-recovered stroke patients, however, it appears that continued ipsilateral recruitment of motor areas may be adaptive.<sup>23,30–32</sup> For example, similar to the present report, Fisher<sup>33</sup> reported two patients with

contralesional motor hemiplegia following stroke. These patients suffered from two separate stroke events that occurred in opposing hemispheres. Following their initial strokes, both patients were regaining strength in their affected limbs when they suffered from another stroke, and their recovering limb became re-paralyzed. The authors proposed that the re-paralysis of the recovering limb suggested that the contralateral corticospinal tract had been contributing to their motor recovery. A transcranial magnetic stimulation (TMS) study<sup>34</sup> also found a significantly larger cortical representation of the hand region in the contralesional motor cortex in stroke patients following rehabilitation. These results further suggest that motor recovery may be the result of the contralesional, undamaged hemisphere assuming the function of the previously damaged region.

While data on stroke recurrence rates are quite variable, studies have reported up to 11.2% of patients having a second stroke within 12 months<sup>35</sup> [as cited in]<sup>36</sup> 15% within two years,<sup>37</sup> and 9.5% within 5 years after transient ischemic attack or mild ischemic stroke.<sup>38</sup> Another comprehensive study found that the risk of recurrence was 1.2% in the first 30 days, 3.4% within 90 days, 7.4% within 1 year, and 19.4% within five years.<sup>36</sup> A review investigating the patterns of recurrent strokes found that patients with an initial cardioembolic stroke experience second stroke of the same type most often, followed by those with initial non-lacunar non-cardioembolic stroke, hemorrhagic stroke, and lacunar stroke (77%, 65%, 58%, and 48%, respectively).<sup>39</sup> In patients with initial hemorrhagic stroke, 42% of the second strokes were ischaemic, whereas patients with initial ischaemic stroke only occasionally suffered а second hemorrhagic stroke (5%).

Unfortunately, there does not appear to be any studies describing the likelihood of a second stroke occurring in the opposite hemisphere. The present case report describes a rare case of a patient with an initial ischemic stroke in the right hemisphere followed by a second hemorrhagic stroke in the left hemisphere.

#### Case report

A 61-year-old left hand dominant woman presented with altered level of consciousness following a fall down two flights of stairs. She had texted her friend regarding her fall and then begun to send incomprehensible messages.

Past medical history included hypertension, diabetes, psoriatic arthritis and right frontal stroke in February of 2016. After treatment in the local hospital for her stroke, she was admitted to a care home, and received three months of rehabilitation. At the time of discharge, she was independent and was able to live at home by herself. Her medications included metformin, metoprolol and Plavix.

On examination, she was intubated and ventilated. She had a GCS of 6 (E1VTM4). Her pupils were 4 mm and sluggishly reactive bilaterally. CT scan was done, which showed an acute, left-sided subdural hematoma (Fig. 1). She was taken for decompressive hemicraniectomy, which proceeded without incident. Post-operatively, she was sent to the ICU. Her course in the ICU was uneventful, and she was transferred to the ward after extubation. Following transfer to the ward, she developed issues with refractory left-sided seizures, and had to return to the ICU for seizure control. This was achieved with Dilantin 100 mg po TID and Keppra 1000 mg po BID. After seizure control she continued to have severe postictal left-sided

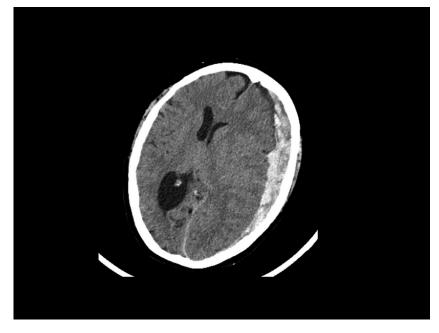


Fig. 1. CT scan image revealing large left subdural hematoma.

weakness. Her right side remained normal in strength throughout her course.

Following this, fMRI localization of motor processing was performed in order to determine whether the patient had ipsilateral motor activation (i.e., left M1 activation for left-sided motor movements) given her ipsilateral symptomology. Functional tasks that have been shown to provide diagnostic utility for motor cortex mapping were used to determine the regions of activation for hand, arm, and foot movement.<sup>40,41</sup> Diffusion tensor imaging (DTI) tractography was also collected to visualize the motor and sensory tracts. Following the cranioplasty the patient was transferred to rehabilitation. The patient's consent was obtained and the scan was performed in compliance with the Declaration of Helsinki (2008) and the relevant laws and institutional guidelines and the University of Saskatchewan Research Ethics Board.

The patient did well following seizure control, and was sent to inpatient rehabilitation. She returned two months post-operatively in order to have cranioplasty. Her cranioplasty was performed routinely, but once the myocutaneous flap was dissected from the dura we performed cortical mapping, which is detailed separately below. This showed partially bilateral and partially ipsilateral motor innervation. Post-operatively, the patient did well and returned to inpatient rehabilitation on post-operative day three.

#### Materials and methods

*fMRI Protocol.* All imaging was conducted using a 3 Tesla Siemens Skyra scanner. Whole-brain anatomical scans were acquired using a high-resolution magnetization prepared rapid acquisition gradient echo sequence consisting of 192 T1-weighted echo-planar images (EPI) slices of 1-mm thickness (no gap) with an in-plane resolution of  $1 \times 1$  mm (field of view 256 × 256; TR = 1900; TE = 2.08). For each of the functional tasks, T2\*-weighted single shot gradient-echo EPI scans were acquired using an interleaved ascending sequence, consisting of 105 volumes of 25 axial slices of 4-mm thickness (1-mm gap) with an in-plane resolution of 2.65-mm × 2.65-mm (field of view = 250) using a flip angle of 90°. The top 2 coil sets (16 channels) of a 20-channel Siemens head-coil were used.

*DTI protocol.* Thirty non-collinear directions of diffusion-sensitizing gradients were acquired, diffusion sensitivity  $b = 1000 \text{ s/mm}^2$ , TR = 3700 ms, TE = 95 ms. Twenty-five, 4 mm thick axial slices were obtained. The voxel resolution was  $1.72 \times 1.72 \times 4$  mm, with a field of view of 220 mm and an acquisition matrix of  $128 \times 128$ .

Stimuli and fMRI tasks. The stimuli were presented using a PC running EPrime software (Psychology Software Tools, Inc., http://www.pstnet.com) through MRI compatible goggles (Cinemavision Inc., http://www.cinema vision.biz). The leading edge (10  $\mu$ s) of the fiber-optic signal that is emitted by the MRI at the beginning of each acquisition volume was detected by a Siemens fMRI trigger converter and passed to the EPrime PC via the serial port. As such, perfect continuous synchronization between the MRI and the experimental paradigm computer was obtained at each volume. For the motor tasks, the patient viewed a fixation cross for the rest periods and the word "TOUCH" appeared on the screen indicating for the patient to perform the movement.

*Motor tasks.* The patient performed six motor tasks: Right hand movement, left hand movement, right arm movement, left arm movement, right foot movement, and left foot movement. The patient performed five blocks with five trials per block for each sensory/motor task.

*fMRI analyses*. All preprocessing and statistical analyses for functional images were performed using Brain Voyager QX (www.brainvoyager.com). Functional images were preprocessed and corrected for slice scan time acquisition (cubic spline interpolation), 3D motion correction (trilinear/sinc interpolation), and temporal filtering with a high-pass filter to remove frequencies less than two cycles/time course. Spatial smoothing was implemented in BrainVoyager by applying a 3D Gaussian kernel 6 mm in width to the data. The first five image volumes were used to achieve steady state of image contrast and were discarded prior to analysis.

*DTI analyses.* Tensors were reconstructed and tracked from 30-direction diffusion MR images using Diffusion Toolkit Software Version 0.6.4 and visualized using TrackVis Software version 0.6.1. The angle threshold was set to 30°. Tracts were preprocessed using a spline filter to remove redundant tract points and segments. T1-weighted image maps were used as an underlay for anatomical visualization. The measures that were collected from the DTI analyses included: 1) Fractional anisotropy (FA), which is a metric that quantifies the extent to which water diffusion is directionally restricted; and 2) Mean diffusivity (MD), which is a scalar measure of the total diffusion within a voxel, and are commonly used clinically to localize white matter lesions; 3) Number of tracts; and 4) Average length of the tracts.

# Neurophysiological examination during cranioplasty

The cranioplasty was performed using an intravenous anesthetic with a protocol that allowed for motor cortical mapping. A bipolar stimulating probe (NIM-Eclipse 3; Medtronic of Canada, Mississauga, ON, Canada) was connected to an intraoperative neuromonitoring system (NIM-Eclipse 3, Medtronic of Canada, 2020). Recording electrodes were placed in upper and lower limb muscles bilaterally. Stimulation was applied at 4–6 mA at each of five locations on the surface of the brain that were believed to represent motor function. On one location, right sided motor responses were seen in the upper limb. In the remaining four locations, left sided (ipsilateral) responses were seen in both upper (three locations) and lower (one location). Peripheral nerve stimulation was used to confirm the placement of the electrodes.

#### fMRI results

*Hand movement*. In Fig. 2a, using a linear correlation threshold of r(97) = 0.60, p < .001, right hand movement resulted in unilateral activation of the left M1. Fig. 2b, using a linear correlation threshold of r(97) = 0.60, p < .001, left hand movement resulted in bilateral activation in both the left and right M1.

*Arm movement.* In Fig. 3a, using a linear correlation threshold of r(97) = 0.54, p < .001, right arm movement resulted in unilateral activation in the left M1. Fig. 3b, using a linear correlation threshold of r(97) = 0.54, p < .001, left arm movement resulted in bilateral activation in both the left and right M1.

*Foot movement.* In Fig. 4a, using a linear correlation threshold of r(97) = 0.52, p < .001, right foot movement resulted in unilateral activation in the left M1. Fig. 4b, using a linear correlation threshold of r(97) = 0.52, p < .001, left foot movement resulted in bilateral activation in both the left and right M1.

#### **DTI results**

*Corticospinal tract.* The DTI results showed that the corticospinal tracts (CST) were within normal limits and showed no displacement or disorganization (Fig. 5). The relative fiber density was 71 for the right and 50 for the left CST. The right CST had an average length of 112.71 mm

*Spinothalamic tract.* The DTI results also revealed that the spinothalamic tracts (STT) were within normal limits and showed no displacement or disorganization (Fig. 6). The relative fiber density was 67 for the right and 66 for the left STT. The right STT had an average length of 124.71 mm (sd = 40.04 mm), an FA value of 0.42, and a MD value of 0.93. The left STT had an average length of 117.98 mm (sd = 38.28), an FA value of 0.42, and an MD value of 0.92.

#### Discussion

A possible contribution of the ipsilateral hemisphere for restoration of motor functioning following stroke recovery has been observed in several clinical reports and neuroimaging studies.<sup>1-4</sup> The present case report demonstrated contralateral fMRI activation for movements of the unaffected side of the body, however, consistent bilateral fMRI activation was shown for movements of the affected side of the body. These findings are presumably due to reorganization of the motor cortices following the patient's initial right-sided stroke. During this reorganization, the left (unaffected) M1 may have become involved in moving the left side of the body. Thus, the second episode of a left subdural hematoma may have caused left-sided hemiparesis. More specifically, through the recovery of the left side of their body the patient may have developed simultaneous

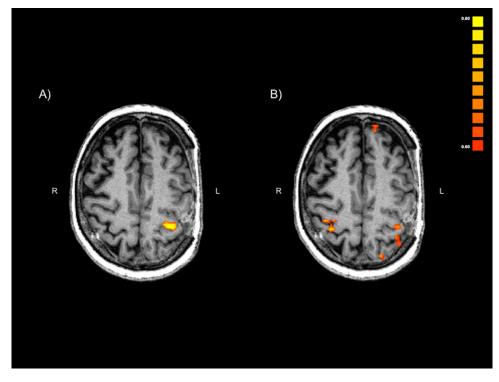


Fig. 2. a) fMRI activation in the left M1 for right hand movement b) fMRI activation in bilateral M1 for left hand movement.

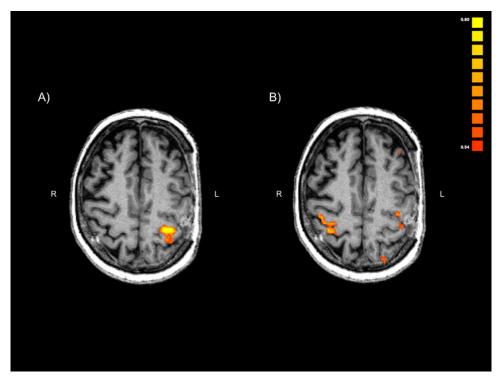


Fig. 3. a) fMRI activation in the left M1 for right arm movement b) fMRI activation in bilateral M1 for left arm movement.

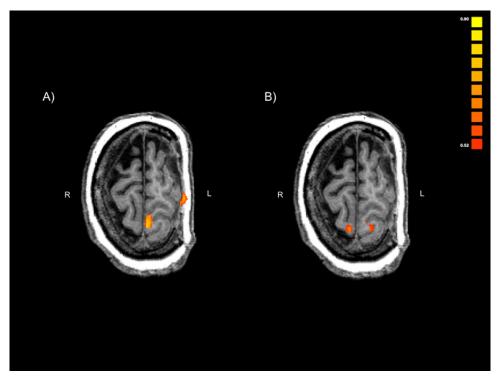


Fig. 4. a) fMRI activation in the left M1 for right foot movement b) fMRI activation in bilateral M1 for left foot movement.

coordination between both hemispheres. Thus, the second hemorrhage may have disrupted the coordination between the ipsilateral and contralateral hemispheres (given that it involved regions including the motor cortex), resulting in loss of function of the left side. The fMRI results were also supported by intraoperative cortical mapping, whereby ipsilateral EMG responses were found for stimulation of the left M1.

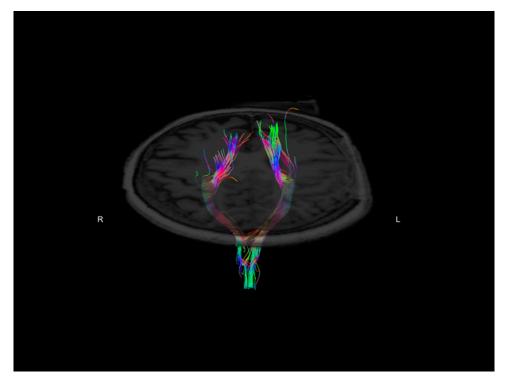


Fig. 5. DTI showing corticospinal tracts within normal limits and displaying no displacement or disorganization.

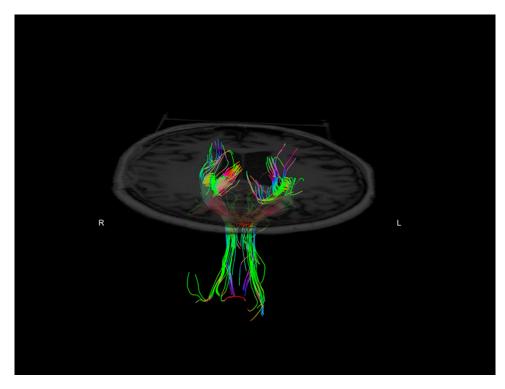


Fig. 6. DTI showing spinothalamic tracts within normal limits and displaying no displacement or disorganization.

Cortical reorganization of sensorimotor areas has been shown to be highly plastic.<sup>2</sup> In general, cortical reorganization has been attributed to cortical redundancy, changes in synaptic strength, synaptogenesis, assumption of function by contralateral homologous cortices, and recruitment of ipsilateral adjacent regions.<sup>1,2,42</sup> In the present study, the finding of bilateral fMRI activation in M1 for left-sided motor movements (i.e., affected limbs) supports the notion that functionally relevant adaptive changes can occur in the brain following focal damage from stroke. Specifically, homologous brain regions can be recruited to facilitate motor recovery. Several mechanisms may be responsible for these adaptive changes. It may be the case that rehabilitation of hemiparetic limbs induces an amplification of normal cortical activity associated with related motor activity. It has been shown that the ipsilateral motor cortex participates in controlling complex and fine-scale hand movements in healthy participants,<sup>43–47</sup> and elevated ipsilateral activity following stroke may reflect the assumption of a greater role in general limb movement by the ipsilateral motor cortex.<sup>16</sup> In contrast, reorganization may be in response to reduced functionality in the cortex affected by stroke. Ipsilateral cortical activity in normal patients has been shown to be inhibited in part by contralateral cortical activity during limb movement,<sup>48</sup> potentially in order to reduce activation of the motor cortex in controlling the opposite limb.49,50 Experimental animal studies suggest an additional mechanism responsible for cortical reorganization, specifically that stroke may directly and spontaneously induce synaptogenesis in the unaffected motor cortex, which can be reinforced during post-stroke training and motor recovery, thus enhancing structural reorganization of ipsilateral motor cortices.<sup>51,52</sup> Specific mechanisms responsible for cortical reorganization likely vary and may play combined roles in given cases that will only be resolved through further investigation. Nevertheless, it is clear that atypical cortical organization occurs, which has immediate and important relevance to motor recovery in stroke patients.

The functional role of the contralesional M1 has been under debate.<sup>20,53,54</sup> However, it is likely that brain regions both ipsi- and contralateral to the stroke are involved in cortical remodelling and recovery.27,28,55,56 Anatomically, the ipsilateral hemisphere could contribute to motor recovery through direct (uncrossed) fibres of the corticospinal tract.<sup>57</sup> Bastings et al.<sup>58</sup> found that the persistence of a functional pyramidal tract seems necessary for recovery to occur after a cortical stroke. Braun et al.<sup>59</sup> also found that crossed CST connectivity underlined motor recovery in patients with subcortical stroke. They proposed that maintaining or regaining use of crossed CST fibers is one way to achieve effective recovery. Together, these findings suggest that structural changes of ipsi- and contralesional white matter and in cerebral cortex occurs after stroke and relate to motor recovery.

Consideration of variables such as extent of damage, size and lesion location, and type of motor task can help illustrate the role of the contralesional hemisphere in functional recovery.<sup>6,60,61,62</sup> In more severely impaired patients, for example, ipsilateral recruitment may be compensatory to account for the damaged region according to TMS and fMRI studies.<sup>23,32,63,64,65,66</sup> Experimental studies in rat models suggest a positive relationship between lesion size and contralesional activation.<sup>67,68</sup> In a study examining acute stroke patients,<sup>32</sup> followed stroke-induced changes in motor system activity over two weeks. Degree of initial impairment proved a key differentiating factor in cortical reorganization patterns; in severely affected patients only, gradually increasing activity in the contralesional primary motor cortex and the premotor cortex correlated with improved functional recovery. Studies including chronic stroke patients similarly indicate the participation of the contralesional hemisphere. Schaechter and Perdue<sup>65</sup> demonstrated increased ipsilateral cortical activity in patients ( $\geq 6$  months post-stroke) with good motor recovery and Weiller et al. <sup>66</sup> found a similar effect for patients with chronic striatocapsular motor strokes ( $\geq 2$  months post-stroke). For a thorough reviews of functional reorganization of motor regions, as well as further discussion of the distinct variables determining post-stroke recovery are available <sup>6,55</sup>

Restoration of function in patients with hemiparesis following stroke has important implications for rehabilitation given that paralysis is a major source of physical and mental hardship among stroke patients and caregivers. The possibility of recovery of strength in hemiparetic limbs may be higher than expected given cortical reorganization, and understanding mechanisms that facilitate reorganization are critical in developing effective rehabilitation techniques and adjusting expectations for patients and medical experts.

#### Conclusions

The findings reported in the present case report support the notion that cortical reorganization occurs in stroke patients recovering from hemiparesis, and specifically, provides converging evidence that components of motor processing subserved by M1 may be taken over by ipsilateral regions. Bilateral activation, and specifically activation in the ipsilateral hemisphere for movement of the affected limbs, strongly suggests that reorganization played a critical role in restoring the patient's motor function and that the unaffected hemisphere provided capacity for increased stroke recovery. These findings also provide further understanding of cross-education effects and inter-hemispheric transfer for motor skills. A greater understanding of neural plasticity following injury may potentially improve the recovery process and facilitate the development of novel therapeutic techniques that are based on neurobiological principles designed to minimize impairment in appropriately targeted patients suffering from hemiparesis following stroke.

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#### **Declaration of Competing Interest**

None.

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